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Editorial

Chance, choice and cause in cancer aetiology: individual and population perspectives

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Introduction

‘Cancer is down to ‘bad luck not lifestyle’. Experts claim 65 per cent of cases are random”¹—the headline in the British tabloid newspaper, the *Daily Express*—was typical of the extensive media coverage of a *Science* paper,² published in 2015, that related the lifetime risk of particular types of cancer in the USA to the number of stem cell divisions occurring in the tissues from which these cancers arise. ‘The majority of cancer cases are down to sheer bad luck, rather than unhealthy lifestyle, poor diet or even inherited genes, according to a new study,’¹ the story continued. ‘All cancers are caused by a combination of bad luck, the environment and heredity, and we’ve created a model that may help quantify how much these three factors contribute to cancer development’,³ Bert Vogelstein, the senior author and a leading cancer researcher, said. *The Guardian*’s Owen Jones found it ‘liberating’ that ‘the majority of cancers are down to chance’.⁴ Lifestyle, environment and heritable genetic variation had all been over-played as contributors to cancer risk, it was agreed, and screening, early detection and treatment were the way to go.

These bold and confident conclusions cannot be attributed to the simplifications of over-enthusiastic journalists, as some have attempted to do.⁵ A *Time* magazine article produced a graphic representation of the types of cancer that could be categorized as due to ‘bad luck’ in contrast to those that could be considered as attributable to ‘bad luck plus environmental and inherited factors’ (Figure 1).⁶

In *Science* itself, the sub-heading of the *In Depth* commentary⁷ on the paper was ‘analysis suggests most cases can’t be prevented’, and readers were told that ‘the average cancer patient ... is just unlucky’, and that ‘cancer... often cannot be prevented, and more resources should be funnelled into catching it in its infancy’. The media coverage simply reported what the journal and the authors had stated.

As is often the case, the conclusions from a single study were not viewed against the background of the broader scientific literature and established facts. Stark discrepancies between the interpretations of this one study and evidence of the potential preventability of cancer emerge in this light. The starting point here are epidemiological data on variations in cancer risk over time and between different places and how cancer rates change upon migration. Clearly changes in luck cannot lead to dramatic increases or decreases in cancer rates over time, or large differences in risk between different countries. Yet this is precisely what is seen.

Lung cancer was a medical rarity in the early 20th century in the USA, representing less than 1% of all cancer cases in a 1914 report of over 50 000 cases from the U.S. Bureau of the Census. By contrast, stomach cancers accounted for over 20% of all cancer cases. Lung cancer rates increased by orders of magnitude as a consequence of the adoption of cigarette smoking, whereas stomach cancer rates declined dramatically across the 20th century (Figure 2).⁸ The reduction in stomach cancer rates was a

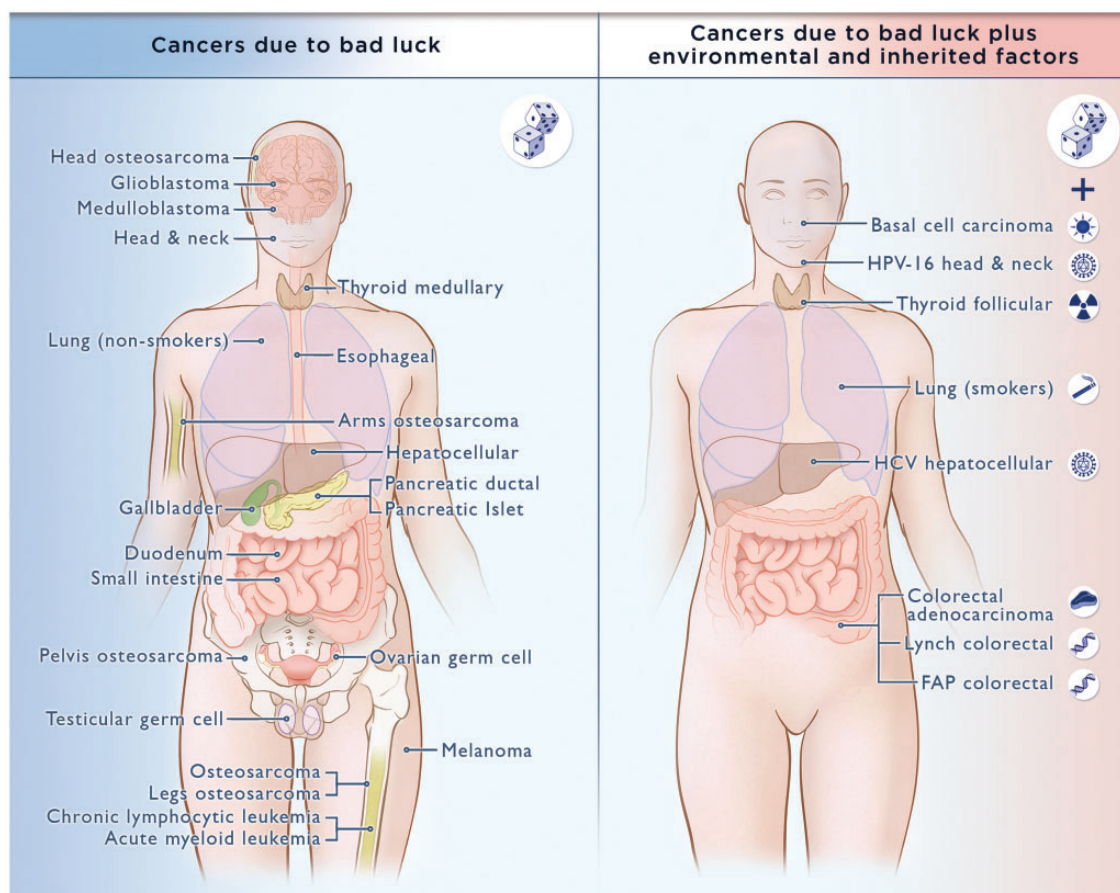


Figure 1. Cancers attributed to bad luck in popular media coverage⁶ of the Tomsetti and Vogelstein paper².

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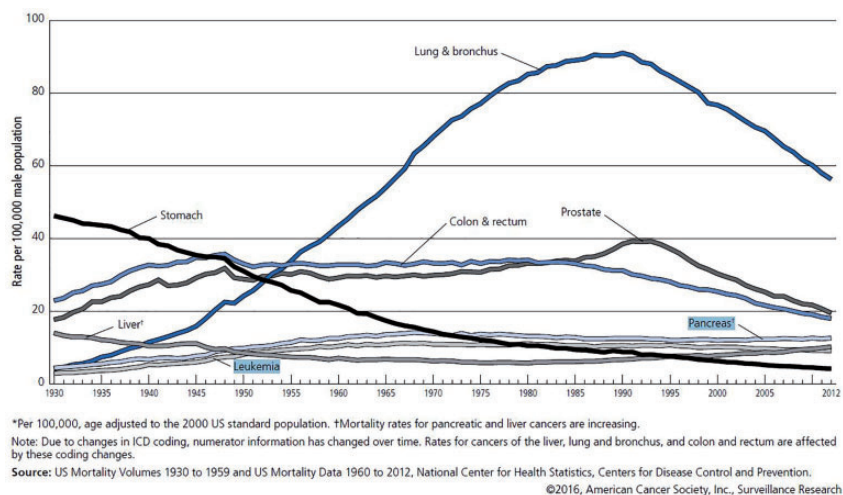


Figure 2. Trends in age-adjusted cancer death rates* by site, males, USA, 1930–2012.

likely consequence of equally marked reductions in infection by the bacteria *H pylori*, a probable partial consequence of the introduction of the domestic refrigerator in the early part of the 20th century (Figure 3), together with

other factors leading to decreases in faecal-oral transmission of bacterial infection in infancy and childhood.⁹

Similar malleability of risk is indicated by the large differences in rates of cancer across countries (Figure 4),¹⁰

She says
it's
"the best"

She says
it's
"the best"

INFANT MORTALITY would be GREATLY REDUCED

If all homes were equipped with BOHN SYPHON REFRIGERATORS. This statement by medical authority will not appear exaggerated when it is considered that the great majority of the ills of early life are directly attributed to impure milk.

The BOHN SYPHON REFRIGERATOR

lined or entirely constructed of material like the best white enameled kitchen-ware, is absolutely cleanly. The Syphon System creates a vigorous circulation of the air within, which is dried and purified by the condensation of all impurity-laden moisture within the ice chamber. This produces a dry cold 10 degrees lower than in any other refrigerator—a temperature absolutely necessary for the perfect preservation of food. The fact that the Pullman Company and all railroads equip their dining cars with Bohn Syphon Refrigerators is evidence of the economy and efficiency of the system.

Send for "Cold Storage in the Home," free. Shows how milk can be kept with onions without contamination.

**WHITE ENAMEL
REFRIGERATOR CO.**

Main Office and Works, St. Paul, Minn.
New York Office and Salesroom
59 W. 42nd St.

Figure 3. Infection reduction through refrigeration? A newspaper advertisement from the early 20th century might have been correct in its claims regarding the effect of refrigeration on infant infection (and infant mortality), with consequent reductions in stomach cancer many decades later, reflecting the protection against early life infection by *H. pylori* provided by such innovations.

with risk also changing with migration between countries. These basic approaches of establishing time trends, geographical differences and the influence of migration on cancer risk cannot be due to chance or luck—or direct genetic effects, for that matter. Contrasts between rates in low- and high-risk populations set a benchmark for the degree to which environmental influences are causing a particular cancer, and what is preventable in principle.

In their 1981 report on the causes of cancer,¹¹ Richard Doll and Richard Peto provided an estimate of the proportion of cancers that could be theoretically avoided by comparing rates in Connecticut (an established US cancer registry) for each cancer site, with the lowest rates found in

a reputable cancer registry elsewhere (published in the 1976 version of the third edition of the IARC publication *Cancer Incidence in Five Continents*, covering the period around 1967–71).¹² For example, the lowest liver cancer or melanoma rates at that time were observed in the UK, and the lowest lung cancer rates in Nigeria. Doll and Peto concluded that 75–80% of cancers are likely to be avoidable, although this statistic could be higher. Conducting a similar exercise now, based on registry data from 2003 to 2007 and comparing the Connecticut cancer registry data with the lowest fifth percentile of other cancer registries, provides a broadly similar result (79% of female and 83% of male cancers being avoidable). One could select the

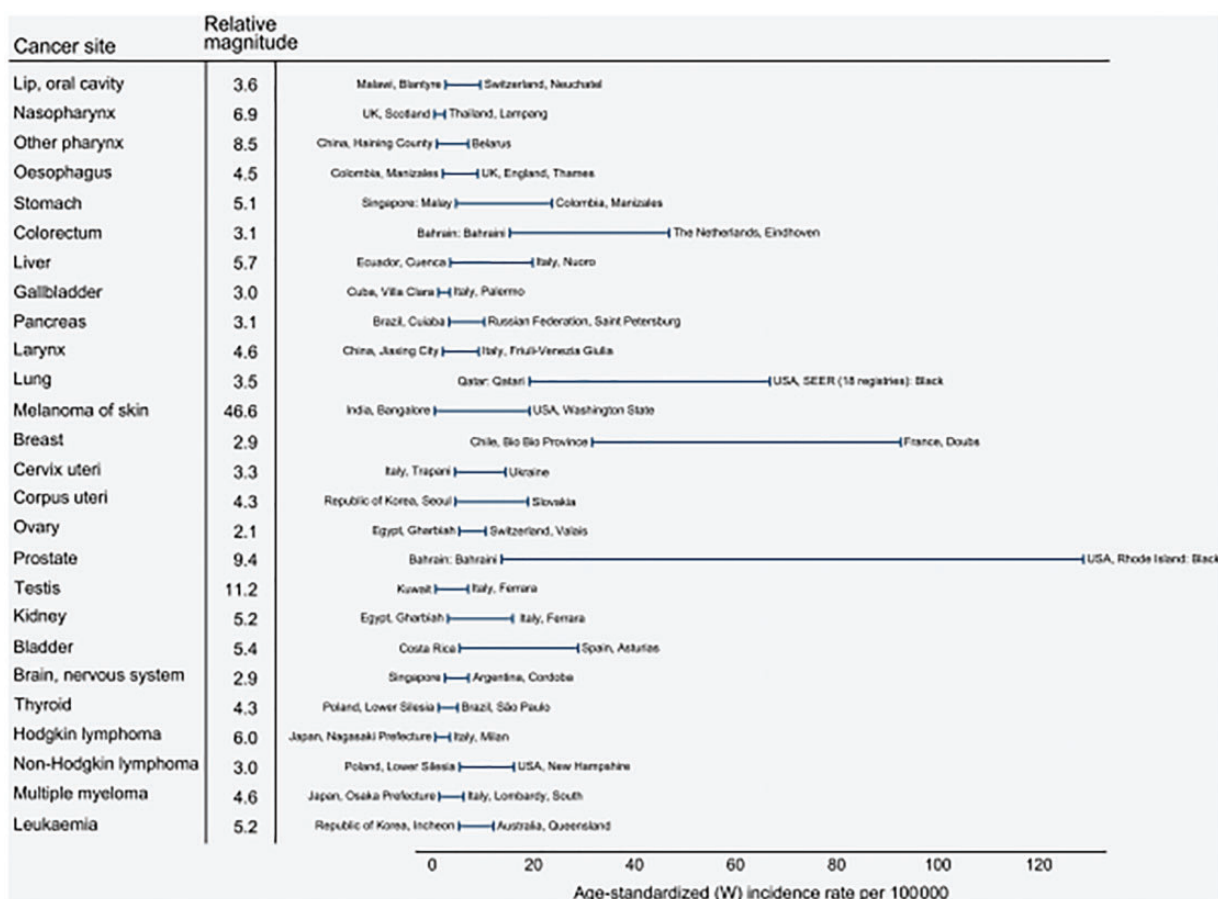


Figure 4. Rates of cancer across high-quality cancer registries across the world. From Bray *et al.* (2015).¹⁰

lowest recorded incidence rate for each cancer site for this calculation (i.e. below the fifth percentile), although the message will remain similar. The vast majority of cancers are caused by modifiable exposures (some known, some not) and are not simply down to bad luck.

What can be leading to the mismatch between the apparent conclusions of the *Science* study and this well-established evidence of the modifiability of cancer risk? Considering that the role of luck in cancer has been widely recognized and discussed for decades, why did it re-emerge? Ironically, almost exactly the same conclusions as were given by Tomasetti and Vogelstein had been reached by William Cramer 80 years previously, when he wrote in the *Lancet* that ‘the reason why cancer appears to be a mysterious disease is its apparently capricious incidence: in the majority of cases we do not know why one individual develops cancer and another remains free from it, although living under apparently the same conditions. Our ignorance on this point makes it impossible to prevent the disease’.¹³ Responding to Cramer, J. P. Lockhart-Mummery wrote ‘...the chances of being able to prevent cancer... is not a very hopeful one... however... if individuals are carefully examined at regular intervals, there is an

excellent chance that they should be detected at an early stage, when it is curable’,¹⁴ echoing the conclusions drawn eight decades later on the basis of the Tomasetti and Vogelstein paper, regarding the apparent need to divert resources from prevention to early detection.^{2,7}

In reality, over these 80 years there had emerged a general (although clearly not universally appreciated) understanding that there is actually no mismatch between a high proportion of cancer cases being preventable in principle, whereas at an individual level cases appear sporadic, to the extent of being apparently quasi-random.¹⁵

What was known before this study?

The large majority of cancer cases arise from tissues that undergo cell divisions throughout life, in particular from epithelial tissues. Epithelium covers the external surface of organs that are linked directly to the external world (e.g. skin, intestinal linings, bronchi in the lungs, the cervix) or internal surfaces of ducts and tracts with a less direct link to the outside environment (e.g. breast ducts, prostatic ducts, the bladder, ovary, pancreas, etc.). Thus the common cancers—which contribute most to the overall

burden of cancer—including lung, breast, prostate, colon, cervix and skin—are epithelial. Interestingly, it is epithelial cancers that tend to show most geographical and temporal variation in their occurrence, implicating environmental influences in their aetiology.

There are many generally rare cancers arising from non-epithelial tissues (leukaemia and sarcomas are examples), but these contribute a much smaller proportion of all cancer cases in a population, generally less than 10%. The latter class of cancers includes several types seen in infancy and childhood, which generally arise while the tissues are still dividing during early (particularly fetal) growth and development.¹⁶ The fact that cancers preferentially arise from tissues in which cell divisions occur frequently has been widely recognized for many decades, and was eloquently discussed by Richard Peto in an insightful paper from 40 years ago¹⁷ which we reprint (for the first time without a series of omissions and errors) in this issue of the *IJE*.¹⁸ However, from a public health perspective the key issue relates not to which cancers are more common or rare, but rather to what is the overall burden of cancer, how much of this is preventable in principle, and how much with current knowledge? The difference between the two is an indicator of the need for further research to identify causes of cancer modifiable at the population level (Box 1).

The place of chance, luck or stochasticity in the risk of cancer for any particular individual is widely recognized. One obvious indicator of this relates to cancer in bilateral organs, for example breast or testicular cancer, following a sporadic initial case. Both of a pair of organs share germline genetic make-up and will have experienced almost identical environments (for example, being exposed to the consequences of diet, smoking, occupation and environment). Yet the risk of cancer arising in the contralateral breast or testicle, although raised over the background level, is not dramatically elevated. What can have contributed to one breast or testicle, and not the other, having developed cancer? Some process that we may as well call chance or luck is likely to have been involved.

The distinction between chance at the individual level and modifiable risk at the population level can be illustrated with a simple thought experiment. Take two geographically distinct but demographically similar cities—Lyon and Bristol, for example—and imagine that in Lyon every adult without exception was made to smoke 20 cigarettes a day, whereas in Bristol no one was allowed to smoke a single cigarette. Over the subsequent 50 years, the incidence of lung cancer in Lyon would increase greatly and would become very considerably higher than in Bristol. However within Lyon, where everyone was a smoker, only a proportion of the population would

develop lung cancer, and both those who did and those who did not acquire lung cancer would have smoked exactly the same amount. Within Lyon luck would be a major contributor to which individuals developed lung cancer, but between Lyon and Bristol essentially every additional case could be attributed to smoking, and would have been preventable. In this setting, at the individual level chance plays a major role in deciding who does or does not get cancer, but this does not detract from the major modifiable exposure, smoking in this instance, being responsible for virtually every case of the disease.¹⁵

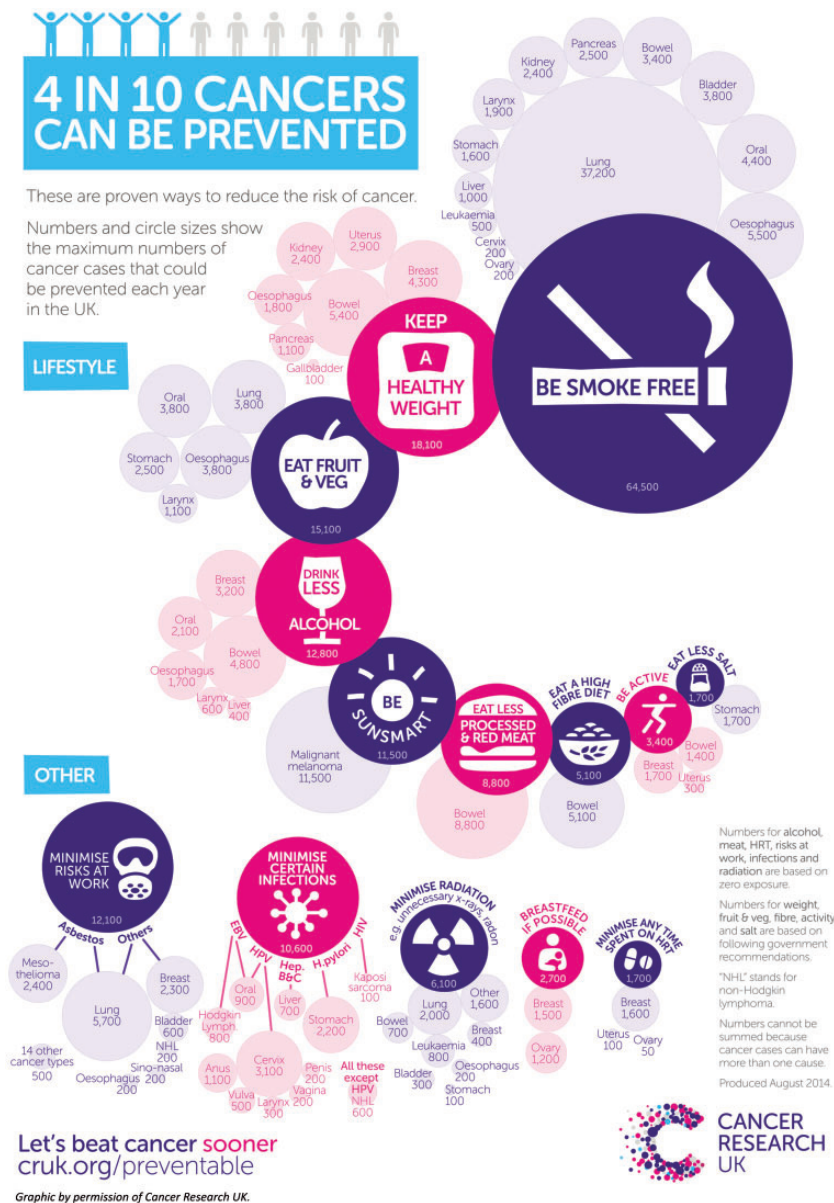
This notion of modifiable exposures coupled with individual-level chance in the context of lung cancer is articulated lucidly in a letter from Richard Peto, published in the *New Scientist* in 1977 (Box 2). In the case of Johannes Heesters, luck was clearly on his side; after what photographic evidence suggests was a lifelong exposure to cigarette smoking (Box 3), he did not succumb to lung cancer. At the age of 106 he chose to quit smoking for his then 61-year-old wife, reputedly stating that this was so ‘she should have me as long as possible’.¹⁹ Such anecdotes abound, underscoring the role of luck and chance implicit in each individual case of cancer. Importantly, this does not mean that cancer prevention at a population level is implausible.

When is ‘environment’ not environment?

The Tomasetti and Vogelstein paper attracted both considerable media attention and considerable academic reaction.^{20,21,22,23,24,25} Whilst much of the latter was astute there have also been examples of similar, but mirror-image, misunderstandings of the levels of explanation required to reconcile chance at the individual level and causal explanation at the population level. We will consider one example, Stephen Rappaport’s paper entitled ‘Genetic factors are not the major causes of chronic diseases’.²⁶ This focused on germline genetic variation, rather than the somatic mutations consequent on cell division that we have discussed so far. The major contribution in twin studies of the so-called ‘non-shared environment’ to variance in cancer risk was noted, and then this (large) component of variance—which incorporates both the main effects of so-called ‘non-shared environment’ (NSE) and the interaction between genetic influences and NSE—was converted into a population-attributable risk fraction, shown to be large for virtually all conditions. This appears to make a strong case for the environmental causes of cancer, but is predicated on the notion that NSE—those factors that lead monozygotic twins with shared germline genomes and shared early life (and many later life) environmental experiences to be different—can be meaningfully termed ‘environment’. It is, indeed, likely that stochastic

Box 1 Cancer: preventability in principle and preventability in practice.

An issue which, in the UK, influenced the reporting of the Tomasetti and Vogelstein paper was that around the same time in late 2015 a Cancer Research UK (CRUK) report was released saying that, with current knowledge, 4 out of 10 cancers could be prevented. This was looking at preventability in practice rather than preventability in principle, which was (misleadingly) addressed by the Tomasetti and Vogelstein paper.² Many similar estimates (of around 40%) have been provided, for example by Parkin *et al.*³⁹ The similarity of the 4 in 10 and the one-third figure for what could be 'prevented' led to these being conflated in reports, apparently supporting each other, whereas preventability in principle and what can now be prevented are very different things.



processes—including somatic mutations, mitotically stable epigenetic events and chance life history incidents that could not be meaningfully targeted in disease prevention—make up a major component of the NSE.¹⁵ It is unfortunate that the terminology of the 'non-shared environment',

introduced by behavioural geneticists, should be allowed to mislead epidemiology. A (much) longer statement of this is available elsewhere;¹⁵ its author now wishes he had replaced the incomprehensible title 'Epidemiology, epigenetics and the 'Gloomy Prospect': embracing randomness in

Box 2 A letter to the *New Scientist* from Richard Peto commenting on the role of chance in cancer⁴⁰**Cancer risk**

Sir,—It is a common misconception that because many smokers do not develop lung cancer there must be constitutional or environmental reasons why they do not. This misconception appears both in *Monitor* (9 December 1976, p 586) and in CB Goodhart's reply (Letters, 3 February, p 294).

Several different heritable changes are probably all needed to alter a normal epithelial cell sufficiently for it to be able to proliferate unlimitedly and act as the progenitor of a carcinoma.

These separate changes are occurring from time to time in one cell or another at one place or another in the lung epithelium, and they are largely irreversible in the sense that when a cell that has suffered one or more of them divides, two similarly changed daughter cells will result.

The essential role of luck in the process of cancer induction follows if we assume that to get cancer two (or more) such changes must coincide in one cell. Even in AD 3000 when all the details of cellular susceptibility and environmental and metabolic peculiarity have been elucidated, a complete and full description of the process of cancer induction will still require that good and bad luck be invoked to explain why my brother got cancer and I did not.

(One of his changes hit a cell, which, having already suffered the other necessary change years earlier, thereby progressed towards malignancy, while in me that second change hit the cell adjacent to a previously changed cell and was therefore irrelevant. Apart from that one unfortunate event, the number of previously changed cells scattered around my lungs and elsewhere in his lungs are pretty much the same, but I was lucky and he was not.)

Of course, we must try to discover why some people get cancer and others do not; we will thereby discover that smokers are more liable to lung cancer, and how the smoker's risk varies with the duration and style of smoking; we may well also discover roles for aryl hydrocarbon hydroxylases, benzopyrene binding factors, vitamin A deficiencies, and so on.

All this will advance our scientific understanding, but when our scientific understanding is as advanced as possible there will still be unexplained stochastic variation which it will be scientifically worthless to investigate, in exactly the sense that it would be scientifically worthless to ask, once the molecular basis of Mendel's laws is properly understood, what was the reason why a particular child born to two parents each with one recessive gene for red hair did not, in fact, have red hair. He was just lucky.

Richard Peto

Department of the Regius Professor of Medicine, University of Oxford

population health research and practice' with the simpler 'Non-shared environment is (probably) not environment'. Whilst aiming to accentuate the importance of environment is laudable in public health terms, it is probably counter-productive in terms of intervening to improve population health, since it simply denies the reliable perception the public have about influences on disease risk at the individual level.^{15,27,28}

Can we harness chance to inform us about the causes of cancer?

Chance is a fundamental part of our biology and can in fact be harnessed to provide insight into the modifiable causes of cancer. The random (chance) assortment of genes at conception—which Richard Peto discusses in his letter—is one foundation of the Mendelian randomization

approach which allows us to use genes as unconfounded, unbiased proxies of environmentally modifiable exposures (such as smoking, alcohol intake and various dietary factors) and strengthen causal inference about the roles these exposures play in cancer risk.^{29,30} There are an increasing number of examples of the application³¹ of this method in cancer research,^{31,32,33,34} including several papers in this issue of the *IJE*.^{35,36,37,38} However, it is important to note in this context too, that the evidence generated should be interpreted at the group level only, and ultimately tells us little about whether one individual will develop cancer whereas their contemporary will not.

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Box 3: Johannes Heester: a lifetime of smoking without succumbing to lung cancer



Validated life course exposure to cigarette smoke

Johannes Heester quits smoking at age 106

"I did it for love, for my
wonderful wife ...
She should have me as
long as possible"



Photo credit: Peter Bischoff/PB archive/Getty Images

(MC_UU_12013/1 and 2). The authors also receive support from CRUK [grant number C18281/A19169].

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